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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/466,935	12/20/1999	VITALIY ARKADYEVICH LIVSHITS	0010-1070-0	1750

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/466,935	LIVSHITS ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *16 and 17* is/are allowed.

6)☒ Claim(s) *18-23,25-30 and 32-36* is/are rejected.

7)☒ Claim(s) *24 and 31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

[1] Claims 16-36 are pending in the application.

[2] Applicants' cancellation of claims 11-15 and amendment to claims 18, 24, 27-30, and 32 in Paper No. 20, filed 12/30/02, is acknowledged.

[3] Applicants' arguments presented in Paper No. 20 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[4] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, First Paragraph

[5] The written description rejection of claims 18-23, 25, 26, 28-30, 32-36 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 7 of Paper No. 18).

Applicant disagrees (beginning at the middle of page 4 of Paper No. 20) with the Office's argument that the specification fails to provide an adequate number of representative species of the claimed bacteria. Applicant cites MPEP 2163.02 in support of their argument. Applicants further disagree with the Office's argument that the specification fails to provide an adequate description of the genus of claimed bacteria because the bacteria have been described only by functional features. Applicant argues that, contrary to the Office's assertions, pages 14-17 of the specification provides an explicit description of the amino acid sequences of the protein, examples of DNA molecules encoding therefor, and methods for increasing or enhancing protein activity. Applicant cites the reference of Berg et al. that allegedly teaches a method for increasing copy number by introduction of a plasmid, phage, or transposon and applicants state that the specification provides examples of suitable multicopy vectors. Applicants

conclude that the prior art and specification adequately describe the genus of claimed bacteria. Applicant's arguments are not found persuasive.

The examiner maintains his position that the claimed genus of bacteria has not been adequately described in the specification. It is the examiner's position that the specification teaches only two representative species of such *Escherichia* bacteria, i.e., *E. coli* transformed with an expression vector comprising the polynucleotide of SEQ ID NO:3 or *E. coli* transformed with expression vectors comprising the polynucleotides of SEQ ID NOs:1 and 3. The ability to increase protein activity by overexpression of an encoding nucleic acid by transforming a bacterium with an expression vector comprising said nucleic acid is well-known in the art and has been described in the specification. However, the specification fails to describe bacteria having *any* modifications that result in increased protein activity and optionally enhanced gene expression. The genus of claimed modified *E. coli* bacteria may have a common function, i.e., resistance to feedback inhibition by threonine or homoserine due to increased expression of threonine or homoserine export proteins. However, a skilled artisan would recognize that the two representative species of *E. coli* as described above are insufficient to provide a representative number of species of the claimed genus of *Escherichia* bacteria having any modification(s) that result in increased protein activity and optionally enhanced gene expression. A skilled artisan would recognize that the species encompassed by the claimed genus is highly variant in regards to the modifications to the bacteria resulting in increased protein activity and optionally enhanced gene expression. Based on the three disclosed species of modified bacteria, a skilled artisan would not be able to predict those modifications that may generate a bacterium with the desired result. For inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, more evidence is required to show possession. As no other bacterial modifications have been provided besides overexpression of the encoding nucleic acid sequences via transformation with an expression vector, the specification fails to adequately describe the claimed genus of modified bacteria. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to

sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

[6] The scope of enablement rejection of claims 18-23, 25, 26, 28-30, and 32-36 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 8 of Paper No. 18).

Applicant disagrees (beginning at the middle of page 5 of Paper No. 20) with the Office's argument that the specification fails to enable a skilled artisan to make the entire scope of claimed bacteria. Applicants argue that any *Escherichia* bacterium modified by any method and having any modification(s) to increase the protein activity of the polypeptide of SEQ ID NO:2 and/or SEQ ID NO:4 is within the scope of the claims and that this scope is not too broad and is within the purview of the skilled artisan. Applicant's arguments are not found persuasive. The examiner agrees with applicant's argument to the extent the scope of the claims is so broad as to encompass any *Escherichia* bacterium modified by any method and having any modification(s) to increase the protein activity of the polypeptide of SEQ ID NO:2 and/or SEQ ID NO:4. However, the examiner disagrees with applicant's assertion that the specification provides enablement such that a skilled artisan can make the entire scope of claimed *Escherichia* bacteria. The specification is enabling for an *Escherichia* bacterium transformed with an expression vector comprising the polynucleotide of SEQ ID NO:3 or an *Escherichia* bacterium transformed with expression vectors comprising the polynucleotides of SEQ ID NOs:1 and 3. However, the specification *does not* enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. It is the examiner's position that the specification combined with what is known in the art does not provide enablement for the entire scope of modified *Escherichia* bacteria.

Beginning at the bottom of page 5 of Paper No. 20, applicant argues that one of skill in the art could obtain and use the entire scope of claimed bacteria based on the disclosure augmented with information known in the art without undue experimentation. Applicant asserts the specification discloses that increasing expression of DNA encoding for RhtB (SEQ ID NO:2) or RhtC (SEQ ID NO:4) yields an

increased activity in the bacterium expressing the DNA, thus increasing L-homoserine or L-threonine feedback resistance. Applicant argues that a skilled artisan could screen or isolate other bacterium expressing the protein by determining L-homoserine or L-threonine resistance properties and/or amino acid production. Applicant argues that the specification's failure to state each and every possible method by which the protein's or proteins' activity/activities are increased is not sufficient to support an enablement rejection as applicant asserts methods of increasing a protein's activity are known in the art and, according to MPEP 2164.05(a), applicant argues that these methods need not be disclosed in the specification. Applicant asserts that the examiner's argument that limitations are not in the claims is of no significance. Applicant argues the specification teaches how to make the claimed bacteria. Applicant argues the Office chooses not to recognize that the claimed invention is fully enabled, despite satisfying each criteria and argues that the "amount of experimentation" standard applied by the Office is overly restrictive and cannot find support in case law or the MPEP. Applicant cites MPEP 2164.06 as support for their argument regarding the "amount of experimentation" standard. Applicant's arguments are not found persuasive.

As stated above, it is the examiner's position that the specification combined with what is known in the art does not provide enablement for the entire scope of modified *Escherichia* bacteria and that undue experimentation would be required for a skilled artisan to make the entire scope of claimed modified *Escherichia* bacteria. The examiner disagrees with applicant's assertion that the Office chooses not to recognize that the claimed invention is fully enabled. The examiner has considered the teachings of the specification and the prior art and in view of these teachings, it is the examiner's position that undue experimentation would be required for a skilled artisan to make the entire scope of modified bacteria as described below. The amount or quantity of experimentation "standard" applied in the Office action of Paper No. 18 is, in fact, one of the Factors for determining whether undue experimentation would be required. These Factors are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention,

(5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). The relevant Factors in the examiner's determination of undue experimentation are described below.

- The claims are overly broad: As previously stated, the claims are so broad as to encompass any *Escherichia* bacterium modified by any method and having any modification(s) to increase the protein activity of the polypeptide of SEQ ID NO:2 and/or SEQ ID NO:4 and optionally wherein protein activity is increased by enhancing the encoding gene expression. The modifications to the claimed bacteria resulting in increased protein activity are *not* limited to those well known in the art as described below. In this case, the specification is enabling only for an *Escherichia* bacterium transformed with an expression vector comprising the polynucleotide of SEQ ID NO:3 or an *Escherichia* bacterium transformed with expression vectors comprising the polynucleotides of SEQ ID NOs:1 and 3.
- The lack of guidance and working examples presented in the specification: The specification provides guidance for increasing protein activity resulting in L-threonine and/or L-homoserine resistance by a single working example, i.e., Example 5 at pages 34 and 35 of the instant specification. Example 5 describes increasing protein activity of the polypeptides of SEQ ID NO:2 or SEQ ID NO:4 by transforming an *E. coli* strain with expression vectors comprising SEQ ID NO:1 or SEQ ID NO:3, respectively. Methods of increasing the activity of a protein by overexpression of an encoding nucleic acid via an expression vector are well known in the art. However, the specification and the prior art fail to provide guidance for increasing protein activity by *any* modification to an *E. coli*. The specification and the prior art fail to provide guidance for increasing protein activity by altering the amino acid sequence of the protein of SEQ ID NO:2 or SEQ ID NO:4 and which, if any, amino acid alterations of the proteins of SEQ ID NO:2 or SEQ ID NO:4 may be altered with an expectation of obtaining a bacterium with increased activity of said protein. Those changes that can be tolerated in a protein's amino acid sequence and obtain the desired activity, i.e., increased protein activity, requires a knowledge of and guidance with regard to which amino acids in the protein, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to

its function. The specification and the prior art fail to provide guidance for altering the regulatory elements, e.g., promoter and/or enhancer, of the endogenous gene encoding SEQ ID NO:2 or SEQ ID NO:4 with an expectation of obtaining a bacterium with increased activity of said protein. Those changes that can be tolerated in an encoding gene's sequence or regulatory elements and obtain the desired activity, i.e., increased protein activity, requires a knowledge of and guidance with regard to which nucleotides of the gene, particularly the regulatory elements, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification). *Escherichia* bacteria modified by these methods are encompassed by the instant claims and the specification clearly fails to provide either guidance or working examples for modifying an *Escherichia* bacterium by these methods to obtain the desired bacterium. It appears that, based on applicant's argument, that such methods of modifying bacteria are known in the art (see bottom of page 5 of Paper No. 20). However, the examiner can find no teachings in the specification or the prior art that would guide a skilled artisan to make the entire scope of claimed bacteria, particularly using these methods of modification. The examiner invites applicants to demonstrate that such methods as described above were well known to a skilled artisan. One of skill in the art would recognize that such methods encompass any alterations to an endogenous other guidance that would enable a skilled artisan to increase the activity of the proteins of SEQ ID NO:2 and/or SEQ ID NO:4.

- The high degree of unpredictability of the art: A skilled artisan recognizes the high degree of unpredictability of modifying a bacterium with an expectation of obtaining a bacterium having a desired activity, in this case, increased protein activity of SEQ ID NO:2 and SEQ ID NO:4, particularly in view of the minimal guidance provided by the specification, which shows only by working example increased protein activity by the use of an expression vector. The positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired increased activity are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Similarly, the positions

within a gene's encoding sequence and regulatory elements where nucleotides may be modified with a reasonable expectation of success in obtaining the desired increased protein activity is highly unpredictable. As stated above, since applicant's arguments appear to assert that methods of modifying bacteria by altering encoding endogenous or exogenous genes are known in the art (see bottom of page 5 of Paper No. 20), the examiner invites applicants to demonstrate that such methods were well known to a skilled artisan.

- The quantity of experimentation necessary: While increasing protein activity by transforming a bacterium with an expression vector comprising a nucleic acid encoding said protein is known in the art, it is not routine in the art to screen for bacteria having an increased protein activity by *any* method. Such experimentation would clearly constitute undue experimentation, particularly in view of the broad scope of the claims, the lack of provided guidance in the prior art and the specification, and the high degree of unpredictability in the art. As stated above, since applicant's arguments appear to assert that methods of modifying bacteria by altering encoding endogenous or exogenous genes are known in the art (see bottom of page 5 of Paper No. 20), the examiner invites applicants to demonstrate that such methods were well known to a skilled artisan.

Conclusion

[7] Claims 16 and 17 are in condition for allowance.

[8] Claims 18-23, 25, 26, 27, 28-30, and 32-36 would be allowable if rewritten to overcome the rejections under 35 U.S.C. 112, first paragraph, set forth in this Office action.

[9] Claims 24 and 31 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date

of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for Group 1600 is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652